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New approaches to wipe sampling methods for antineoplastic and other hazardous drugs in healthcare settings

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Abstract

Purpose—At the present time, the method of choice to determine surface contamination of the workplace with antineoplastic and other hazardous drugs is surface wipe sampling and subsequent sample analysis with a variety of analytical techniques. The purpose of this article is to review current methodology for determining the level of surface contamination with hazardous drugs in healthcare settings and to discuss recent advances in this area. In addition it will provide some guidance for conducting surface wipe sampling and sample analysis for these drugs in healthcare settings.

Methods—Published studies on the use of wipe sampling to measure hazardous drugs on surfaces in healthcare settings drugs were reviewed. These studies include the use of well-documented chromatographic techniques for sample analysis in addition to newly evolving technology that provides rapid analysis of specific antineoplastic

Results—Methodology for the analysis of surface wipe samples for hazardous drugs are reviewed, including the purposes, technical factors, sampling strategy, materials required, and limitations. The use of lateral flow immunoassay (LFIA) and fluorescence covalent microbead immunosorbent assay (FCMIA) for surface wipe sample evaluation is also discussed.

Conclusions—Current recommendations are that all healthcare settings where antineoplastic and other hazardous drugs are handled include surface wipe sampling as part of a comprehensive hazardous drug-safe handling program. Surface wipe sampling may be used as a method to characterize potential occupational dermal exposure risk and to evaluate the effectiveness of implemented controls and the overall safety program. New technology, although currently limited in scope, may make wipe sampling for hazardous drugs more routine, less costly, and provide a shorter response time than classical analytical techniques now in use.

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Introduction

Occupational exposure to antineoplastic and other hazardous drugs is a concern for healthcare facilities in the U.S. and worldwide. Workplace contamination with these drugs, especially antineoplastic drugs, is a continuing issue in places where these drugs are prepared and administered to patients (Davis et al. 2011). At the present time, surface wipe sampling is used to determine the level of workplace contamination in healthcare settings where antineoplastic and other hazardous drugs are present (Connor et al. 2016). Wipe sampling can help identify the need for and effectiveness of engineering controls, the effect of improved work practice controls, and what type of personal protective equipment (PPE) is required (Ashley et al. 2011).

In healthcare settings, dermal uptake is considered the most likely route of occupational exposure to most hazardous drugs, especially low-molecular-weight antineoplastic drugs. Wipe sampling is the most appropriate methodology available to evaluate potential worker exposure to these drugs (Kromhout et al. 2000; Fransman et al. 2004, 2005; Hon et al. 2014)). Inhalation of aerosolized droplets or vapors, accidental hand-to-mouth ingestion following contact with contaminated surfaces, and needles or other sharps are also possible routes of exposure (NIOSH 2009). As stated by OSHA, in some cases skin absorption may be a more important route of exposure than inhalation, especially for non-volatile hazardous chemicals which remain on work surfaces for long periods of time and may not be noticed by the employees (https://www.osha.gov/dts/chemicalsampling/data/CH_235600.html). Although not a direct measurement of exposure, wipe samples can provide information about contamination on surfaces which may lead to dermal uptake by workers.

In general, it is assumed that dermal absorption is more likely to occur with drugs with a molecular weight of <500 Daltons and less likely for those >1000 Daltons (Bos and Meinardi 2000; Kimmel et al. 2011). In addition, lipid-soluble compounds more readily penetrate the skin than water-soluble ones and uptake may be enhanced by the use of carrier solvents. Although many antineoplastic drugs are relatively small molecules with molecular weights <500 Daltons, newer antineoplastic drugs, such as monoclonal antibodies, can have a molecular weight >40,000 Daltons, which presumably limit their potential for dermal uptake from contaminated surfaces (Connor and MacKenzie 2011; Alexander et al. 2014; King et al.). N, N-Dimethylacetamide and other solvents used in some drugs may pose an additional health risk and/or may facilitate drug penetration of the skin (Munro and Stoughton 1965).

McDevitt and colleagues at Johns Hopkins Hospital published the first study of surface contamination with antineoplastic drugs in the U.S (McDevitt et al. 1993). In that study, cyclophosphamide contamination was demonstrated in both the pharmacy and patient treatment areas. In the mid-1990s, several studies conducted in the Netherlands were published by Sessink and colleagues (Sessink et al. 1992, 1994a, b, 1997), which measured surface concentrations of several antineoplastic drugs by wipe sampling, including cyclophosphamide, ifosfamide, methotrexate, and 5-fluorouracil. As in the U.S. study, surface contamination with these drugs was demonstrated in areas where they were prepared and administered to patients. The studies by Sessink also documented uptake of the drugs

based on their measurement in the urine of healthcare workers. Connor et al. (1999) measured surface contamination in three cancer hospitals in the United States and three in Canada. Their study documented surface contamination with cyclophosphamide, ifosfamide, and 5-fluorouracil in the pharmacy and patient treatment areas, and also in areas adjacent to the pharmacy. Since publication of these initial studies, world-wide reports have been published, demonstrating a universal issue with workplace surface contamination with antineoplastic drugs and uptake of the drugs by healthcare workers. In addition to surface wipe sampling, there have also been a limited number of dermal sampling studies reported in the literature (http://www.cdc.gov/niosh/topics/antineoplastic/). For this review, several relevant studies are discussed in order to describe a framework for wipe sampling for hazardous drugs in healthcare settings.

Although surface wipe sampling is the method of choice to evaluate surface contamination within healthcare settings for antineoplastic drugs, the analytical methodology used for surface wipe sampling and analytical laboratory analysis for antineoplastic drugs has varied considerably (Turci et al. 2003; Connor et al. 2016). This article reviews methodology currently being used for surface wipe sampling for hazardous drugs and discusses new applications of available technology that can be employed to make wipe sampling less expensive and to provide near real-time results for wipe sampling.

Surface wipe sampling methods

Methods for surface wipe sampling have been developed for a number of hazardous agents, such as lead (Brookhaven National Laboratory 1994), asbestos, pesticides, polychlorinated biphenyls (EPA 2007; ASTM 2010), methamphetamine (NIOSH 2011), antibiotics (Nygren et al. 2011), and similar methodology has been applied to sampling for hazardous drugs, primarily antineoplastic drugs (Connor et al. 2016). Although there are many variations in application, some approaches are common to all methods. Once a sampling scheme has been decided upon, it is necessary to determine if methods are available for the drugs of concern. Several laboratories offer analytical services for these drugs and often provide sampling kits for a battery of the more commonly used drugs. Sampling locations tend to be agreed upon, but the surface areas to be sampled can vary considerably, from a “standard” of 100 cm^2 to 500 cm^2 or even larger (Connor et al. 2016). Typically, a commercially available template is used to delineate the wiping area. A suitable solvent is either applied directly to the surface to be sampled or applied to the sampling material. Sampling materials vary among tissues, filter paper, or special sampling swabs, although other sampling media may also work well. The surface is then wiped in a pre-determined pattern, usually in one direction and then perpendicular to that direction. The wiping process may then be repeated for the same location using a second wipe to ensure better recovery (B'Hymer et al. 2015). The wipes are then placed in labelled containers and shipped to the analytical laboratory for analysis. In some case, the samples may have to be shipped on dry ice to maintain drug stability.

Current Analytical methods for antineoplastic drugs

A comprehensive review of analytical methods by Turci et al. (2003) describes some of the sampling and analytical methods that have been employed. These have included gas chromatography (GC), high-performance liquid chromatography (HPLC), and ultra high-

performance liquid chromatography (UPLC); all in combination with mass spectrometry (MS) or tandem mass spectrometry (MS/MS). Inductively coupled plasma mass spectrometry (ICP-MS) has been used for the analysis of total platinum in platinum-based drugs Turci et al. 2003). HPLC with mass spectrometry LC-MS/MS is the current method of choice for analysis of most antineoplastic drugs and does not require derivatization of the drug, as GC methods do (Sessink et al. 1992). Researchers using HPLC-MS/MS are reporting results in the pg/cm^2 range. However, these methods are often very costly and it may take several weeks to obtain results using them. In addition, the number analytical laboratories in the U.S. that can perform these analyses is limited.

Analytical techniques for measurement of surface contamination by antineoplastic drugs such as HPLC–MS/MS are sensitive, specific, and accurate, but the initial equipment investment is high and a trained analytical chemist is required to operate the instrumentation, so these methods often cannot be used on a frequent basis due to cost (Pretty et al. 2012). Also, results from HPLC-MS/MS analyses are often obtained after a long delay, which may result in contamination existing for a long period of time before clean up can take place. Hence, these methods often cannot provide immediate feedback in developing work practices needed to lower exposure due to the time period between sample collection and obtaining the results of the analysis. Immunochemical techniques provide an opportunity for more cost-effective routine measurements and can provide direct reading near real-time on-site measurements.

Immunochemical technique for simultaneous detection of drug surface contamination by multiple drugs

A fluorescence covalent microbead immunosorbent assay (FCMIA) for performing multiple immunochemical determinations simultaneously has been developed by Luminex Corporation. (Fulton et al. 1997, Oliver et al. 1998). FCMIA combines several classical methodologies: immunoassays, microspheres, and flow cytometry technology. In FCMIA, immunoassays are performed on sets of solid support 5.6 μm microspheres with different characteristic internal fluorophores that allow multiple assays to be performed simultaneously (multiplexing). FCMIA has predominantly been used for multiple protein and nucleic acid analytes such as multiple antibodies in serum (Biagini et al. 2003) multiple cytokines in serum (Bower et al. 2009), and multiple RNA and DNA viruses in patient samples. (Ginocchio et al. 2009). FCMIA assays are simple to set up and the instrumentation requires limited training to operate. NIOSH has developed an assay and sampling technique capable of evaluating multiple drugs of abuse on surfaces using competitive FCMIA (Smith et al. 2010), which has been used for exposure assessments in law enforcement evidence vaults where relatively high surface levels were observed in the studies (King et al. 2013; Fent et al. 2012).

A FCMIA has been demonstrated for use in the simultaneous measurement of multiple antineoplastic drugs (Smith et al. 2016). The antineoplastic drug assay uses a competitive assay format similar to the drugs of abuse FCMIA assay, where drug in solution competes with a microsphere bound drug–BSA conjugate for an anti-drug antibody. This results in less antidrug antibody being bound to the microsphere at higher drug concentrations. The

anti-drug antibody bound to the microsphere is detected with a labeled secondary antibody (biotin labeled anti-mouse IgG, (Pierce Biotechnology, Inc., Rockford, IL), which in turn binds a fluorescent label (streptavidin R-PE, Molecular Probes, Eugene, OR). Thus, the streptavidin R-PE fluorescent signal from the microsphere decreases with increasing drug concentration (Smith et al. 2016). The surface is sampled using a swab wetted in wash buffer (PBS-0.1% tween). The sampling is done by carefully wiping the surface with the wetted swab in one direction with an overlapping pattern, then repeating the same wiping pattern in a direction perpendicular to the first direction, and finally repeating the original wiping pattern. The swab is then placed in a vial containing 1 ml of storage/blocking buffer (PBS-1%BSA) and the swab is extracted with vigorous shaking for 2 min. The resulting solution is run in the assay without any further dilution.

In field applications, there was no significant cross-reactivity between these drugs at the ranges studied, indicated by a lack of response in the assay to potentially competing analytes (Smith unpublished data). The limit of detection (LOD) for the three drugs are listed in Table 1. The main use of this assay would be for screening surfaces in pharmacies, patient treatment areas, and other areas in healthcare facilities for contamination by antineoplastic drugs. Of special interest are pharmacy areas such as biological safety cabinets (BSCs) or compounding aseptic containment isolators (CACIs) used for drug preparation as well as nursing areas where drugs are administered to patients. Instrumental methods are more sensitive and specific than this assay for several of the drugs (e.g. 5-FU), but this assay is simple and could be set up to be performed at the worksite to provide more timely results. The components of the assay could be supplied as a kit that requires limited training to use. Use of this assay may provide a lower cost method for routine application.

It would be desirable for the FCMIA assay to screen for contamination for a wider array of drugs. This would require the development of antibodies and drug–protein conjugates for the additional drugs, which is a limitation of the assay. Also, cross-reactivity between the drugs being measured, as well as other drugs that might be present, would have to be assessed. The addition of other drugs would result in minimal increases in the time to perform the assay and the FCMIA assay could be used for more drugs at a relatively low cost.

Onsite detection techniques for drug surface contamination based on lateral flow immunoassay

Direct reading, field portable monitors to measure antineoplastic drugs on surfaces also can be used to help reduce potential exposure of healthcare workers to these drugs. Ideally, monitors need to be portable, near real time, sensitive, and easy to use. Monitors based on lateral flow immune assay (LFIA) fulfill the requirements of portability, sensitivity, rapid response, and ease of use. Lateral flow assays are used in many consumer products such as pregnancy tests and are being used in many point-of-care assays for clinical use (marketsandmarkets.com 2016). The lateral flow assay cassettes typically have two lines, a test line which varies in intensity with the concentration of analyte and a control line which is relatively constant for all samples and has been mainly used to assure that the cassette is working properly (Sajid et al 2015).

Lateral flow assay for antineoplastic drug contamination—The development of LFIAs for antineoplastic drugs was based on prior work done by NIOSH to detect methamphetamine contamination on surfaces (Snawder et al. 2011). The methamphetamine lateral flow cassette along with components for the sampling method is commercially available as a kit from SKC Inc (MethChek 50, SKC Inc., Eighty Four, PA), which uses complete disappearance of the test line as the end point for detection. The methamphetamine kit has been used extensively by first responders such as police to evaluate contamination in sites where methamphetamine labs have been located (Hudson et al. 2008). In a further study of the methamphetamine lateral flow cassettes, comparison of the control line and test line was used as a visual end point and the methamphetamine cassettes were read with an electronic lateral flow reader (Smith et al. 2015). Use of line comparison or an electronic reader results in a more sensitive measurements as well as semi-quantitative evaluation of contamination.

Based on success of the lateral flow methamphetamine detection kit, NIOSH investigated the development of lateral assays for antineoplastic drugs. The first assay developed was for 5-FU (Smith et al. 2015). The wiping pattern was identical to that used in FCMIA. A cotton swab wetted in sampling buffer (in this case PBS- 1% tween) was used and the swab wass extracted in 1 ml sampling buffer. For the 5-FU cassette, line comparison was used as the visual endpoint (Figure 1) since complete disappearance of the test line would have resulted in an end point that was less sensitive than desired. The cassette was also evaluated using the electronic lateral flow reader. The 5-FU assay was evaluated by spiking ceramic, vinyl, composite, stainless steel, and glass surfaces of 100 cm^2 area with 5-FU masses of 0, 5, 10, 25, 50, and 100 ng. The 5-FU cassette is capable of detecting 10 ng/100 cm^2 (0.1 ng/cm^2) using the electronic reader and 25 ng/100 cm^2 (0.25 ng/cm^2) using the visual line comparison method for the surfaces studied. Using measurements from the electronic lateral flow reader, the response from 0-100 ng/cm^2 was fitted using the ratio of the control to the test line such that the cassette response could be used to predict the loading over this concentration range. The response of the cassettes was compared to LC-MS/MS results for the same samples for validation and there was good correlation of the two methods but the slope of the plots of the recovered mass from the 5-FU lateral flow measurement versus that for the LC-MS/MS varied from about 0.43 to 1.07 depending on the surface studied and the mass loading on the surface. In addition to 5-FU, lateral flow assays have been developed for paclitaxel and doxorubicin. The paclitaxel assay detected 50-100 ng/100 cm^2, so it was less sensitive than desired but could be used at higher levels of contamination. The doxorubicin assay detected as low as 10 ng/100 cm^2 but had limited range of response, low line intensity, and longer development time. Our commercial partner has produced an improved doxorubicin antibody and doxorubicin protein conjugate in order to develop an improved assay which is now being tested.

The 5-FU lateral flow assay has been used to evaluate contamination in a limited number of hospital pharmacy and patient treatment areas in a pilot study and has agreed with measurement from LC-MS/MS for most of the samples taken. Ongoing evaluations to provide data for a more comprehensive comparison of the lateral flow assay with LC-MS/MS are underway. A large multinational medical equipment manufacturer has shown

interest in the commercial development of the lateral flow assay and has developed an improved assay for doxorubicin which uses a portable reader that the manufacturer developed.

Future Perspectives

Although the methodology for surface sampling is currently only available for a limited number of antineoplastic drugs, methods can be developed for other drugs depending on the availability of antibodies to them. Both LFIA and FCMIA have proven effective in other uses and settings (Biagini et al. 2003; Smith et al. 2010, 2015) and their applicability to measuring surface contamination with antineoplastic drugs at low levels has been demonstrated (Smith et al. 2015, 2016).

Conclusions

Surface wipe sampling is currently used to evaluate workplace contamination with antineoplastic drugs in healthcare and other settings where the drugs may be present. Using LC-MS/MS, surface levels of a few pg/cm^2 can be measured. However, this method is costly and it may take a few weeks for the results to be reported to the facility, thus delaying necessary cleaning procedures and changes in work practices and engineering controls. In addition, most healthcare facilities do not have the capability to perform these assays in-house and must outsource the analyses. A simple, sensitive near real-time method to measure these drugs on work surfaces would enable healthcare workers and health and safety personnel to perform these measurements and obtain immediate results. Therefore, the results of routine cleaning or for cleaning a spill could be obtained within minutes instead of days or weeks.

USP General Chapter <800> recommends performing baseline wipe sampling for hazardous drugs and periodically afterwards (every six months or as often as needed) (USP 2016). A battery of a relatively small number of available assays that could provide near real-time values for surface contamination would be beneficial to many healthcare other facilities where hazardous drugs are present.

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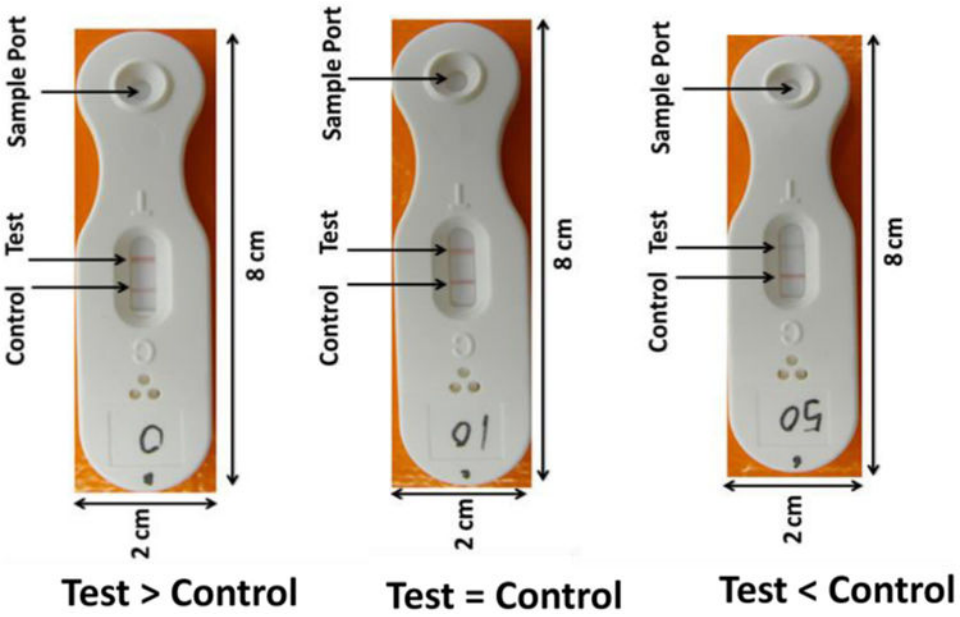

Figure 1. 5-Fluorouracil lateral flow assay cassettes with varying relative test line and control line intensities

Table 1

LOD and LOQ using FCMIA

Drug	LOD (ng/cm^2)	LOQ (ng/cm^2)
5-Fluorouracil	0.93	2.80
Paclitaxel	0.57	2.06
Doxorubicin	0.0036	0.13

From: Smith et al. 2016